(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 773 023 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
14.05.1997 Bulletin 1997/20

(51) Int Cl.[6]: **A61K 31/435**, A61K 31/44, A61K 31/445, A61K 31/505

(21) Application number: **96307977.7**

(22) Date of filing: **04.11.1996**

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE

(30) Priority: **08.11.1995 US 6333**

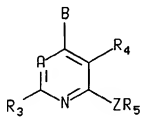
(71) Applicant: **PFIZER INC.**
New York, N.Y. 10017 (US)

(72) Inventors:
- **Chen, Yuhpyng Liang**
Waterford, Connecticut 06385 (US)
- **Fossa, Anthony Andrea**
Mystic, Connecticut 06355 (US)

(74) Representative: **Moore, James William**
Pfizer Limited,
European Patent Department,
Ramsgate Road
Sandwich, Kent CT13 9NJ (GB)

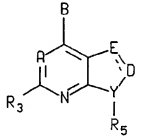
(54) New uses for corticotropin releasing factor (CRF) antagonists

(57) A method of treating, preventing or inhibiting a disorder selected from the group consisting of cardiovascular or heart related diseases such as stroke, hypertension, tachycardia, and congestive heart failure, osteoporosis, premature birth, psychosocial dwarfism, stress-induced fever, ulcer, diarrhea, post-operative ileus, and colonic hypersensitivity associated with psychopathological disturbance and stress, comprising administering to a mammal, including a human, in need of such treatment a therapeutically effective amount of a compound of the formula



I

or



II

or a pharmaceutically acceptable salt thereof, wherein A, B, D, E, Y, Z, R_3, R_4, and R_5 are as defined herein.

EP 0 773 023 A1

Description

Background Of The Invention

The present invention relates to the treatment of certain conditions using a compound of formula I or II, or a pharmaceutically acceptable salt thereof, as defined below. Specifically, the compounds of formulas I and II, and their pharmaceutically acceptable salts, as defined below, exhibit corticotropin-releasing factor (CRF) antagonist activity and are useful in the treatment of cardiovascular or heart related diseases such as hypertension, tachycardia, and congestive heart failure, stroke, osteoporosis, premature birth, psychosocial dwarfism, stress-induced fever, ulcer, diarrhea, post-operative ileus, and colonic hypersensitivity associated with psychopathological disturbance and stress.

The compounds of formulas I and II, their pharmaceutically acceptable salts, and methods of preparing such compounds and salts are referred to in copending PCT international patent application numbers PCT/IB95/00373 (filed May 18, 1995) and PCT/IB95/00439 (filed June 6, 1995), both of which designate the United States, and in copending United States patent applications serial numbers 08/446,539 (filed June 14, 1995) and 08/481,413 (filed June 15, 1995). PCT international patent application numbers POT/IB95/00373 and PCT/IB95/00439, and United States patent application numbers 08/446,539 and 08/481,413, referred to above, are incorporated herein by reference in their entirety.

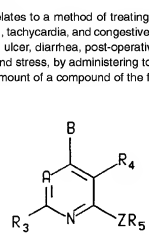
The foregoing PCT international patent applications and United States patent applications refer to the use of the compounds of formulas I and II in the treatment of illnesses induced or facilitated by corticotropin releasing factor and in the treatment of anxiety, depression, fatigue syndrome, gastrointestinal diseases, headache, pain, cancer, immune dysfunction, hemorrhagic stress, drug addiction, drug and alcohol withdrawal symptoms, fertility problems, stress-induced psychotic episodes, neurodegenerative diseases such as Alzheimer's disease; irritable bowel syndrome including Crohn's disease, spastic colon and irritable colon; eating disorders such as anorexia nervosa; and inflammatory disorders such as arthritis, asthma and allergies.

Other CRF antagonists that can be used to treat the disorders recited in the method of this invention are referred to in copending PCT international patent application number PCT/IB95/00318 (filed May 4, 1995), which designates the United States, and in copending United States patent applications serial numbers 08/446,534 (filed June 14, 1995) and 08/448,529 (filed June 14, 1995). PCT international patent application number PCT/IB95/00318, and United States patent application numbers 08/448,534 and 08/448,529, referred to above, are incorporated herein by reference in their entirety.

CRF antagonists are mentioned in U.S. Patents 4,605,642 and 5,063,245 referring to peptides and pyrazolinones, respectively. The importance of CRF antagonists is set out in the literature, e.g., as discussed in U.S. Patent 5,063,245, which is incorporated herein by reference. A recent outline of the different activities possessed by CRF antagonists is found in M. J. Owens et al., Pharm. Rev., Vol. 43, pages 425 to 473 (1991), also incorporated herein by reference.

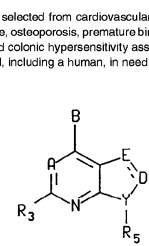
Summary of the Invention

This invention relates to a method of treating a disorder selected from cardiovascular or heart related diseases such as hypertension, tachycardia, and congestive heart failure, osteoporosis, premature birth, psychosocial dwarfism, stress-induced fever, ulcer, diarrhea, post-operative ileus, and colonic hypersensitivity associated with psychopathological disturbance and stress, by administering to a mammal, including a human, in need of such treatment a therapeutically effective amount of a compound of the formula



I

or



II

or a pharmaceutically acceptable salt thereof, wherein
the dashed line represents an optional double bond;

A is $-CR_7$ or N;
B is $-NR_1R_2$, $-CR_1R_2R_{11}$, -C(=CR_1R_{12})R_2, $-NHCR_{11}R_1R_2$, $-OCR_{11}R_1R_2$, $-SCR_{11}R_1R_2$, $-CR_{11}R_2OR_1$, $-CR_{11}R_2SR_1$, -C(S)R_2, $-NHNR_1R_2$, $-CR_2R_{11}NHR_1$ or -C(O)R_2;
D is: (i) N or $-CR_{10}$ when a double bond connects E and D and E is $-CR_4$; (ii) $-CR_{10}$ when a double bond connects E and D and E is N; (iii) $-CR_8R_9$-CHR_{10}-, -C=O, -C=S, -C=NH, or -C=NCH_3 when a single bond connects E and D;
E is $-CR_4$ or N when a double bond connects E and D, and E is $-CR_4R_8$ or $-NR_8$ when a single bond connects E and D;
Y is N or -CH-
Z is NH, O, S, $-N(C_1$-C_2 alkyl) or $-CR_{12}R_{13}$, wherein R_{12} and R_{13} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{12} and R_{13} is cyano and the other is hydrogen or methyl;
R_1 is hydrogen or C_1-C_6 alkyl which is optionally substituted with one or two substituents independently selected from hydroxy, cyano, nitro, fluoro, chloro, bromo, iodo, CF_3, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4alkyl), -S(C_1-C_4 alkyl),-N(C_1-C_4alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -CO_2(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, and (C_1-C_4 alkyl)sulfanyl, and wherein said C_1-C_6 alkyl, C_1-C_4 alkoxy and the C_1-C_4 alkyl moieties in the foregoing R_1 groups optionally contain one double or triple bond;
R_2 is C_1-C_6 alkyl, aryl or (aryl)C_1-C_4 alkyl wherein said aryl and the aryl moiety of said (aryl)C_1-C_4 alkyl are selected from the group consisting of phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, and benzoxazolyl; or R^2 is C_3-C_8 cycloalkyl or (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said (C_3-C_8 cycloalkyl)C_1-C_6 alkyl having at least 4 ring members is optionally replaced by an oxygen or sulfur atom or by $-NR_{14}$ wherein R_{14} is hydrogen or C_1-C_4 alkyl; and wherein each of the foregoing R_2 groups is optionally substituted by from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or by one substituent selected from bromo, iodo, cyano, nitro, C_1-C_6 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfinyl, and (C_1-C_4 alkyl)sulfonyl, and wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_2 groups optionally contain one carbon-carbon double or triple bond;
or R^1 and R^2 of said $-NR_1R_2$ and said $-CR_1R_2R_{11}$ are taken together to form a saturated 5 to 8 member ring, wherein said ring optionally contains one or two carbon-carbon double bonds, and wherein one or two of the ring carbons is optionally replaced by an oxygen or sulfur atom;
R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, SH, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-(C_1-C_2 alkyl), $-CH_2OH$, $-CH_2OCH_3$, -O(C_1-C_4 alkyl), (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfonyl or (C_1-C_4 alkyl) sulfinyl, wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl moieties of the foregoing R_3 groups optionally contain one double or triple bond and are optionally substituted by from one to three substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, -NH(C_1-C_2 alkyl), -N(C_1-C_2)$_2$ -$NHCOCH_3$, fluoro, chloro and C_1-C_3 thioalkyl;
R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, trifluoromethoxy, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2CF_3$, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -N(CH_3)$_2$, $-NHCOCH_3$, $-NHCONHCH_3$, (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, cyano, hydroxy, -CO(C_1-C_4 alkyl), -CHO, or -CO_2(C_1-C_4 alkyl), wherein said C_1-C_6 alkyl, C_1-C_6 alkoxy and the C_1-C_4 alkyl moieties of the foregoing R_4 groups optionally contain one double or triple bond and are optionally substituted with one substituent selected from hydroxy, amino, $-NHCOCH_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -CO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, (C_1-C_3 alkyl)sulfanyl, fluoro, chloro, cyano and nitro;
R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, pyridinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, wherein said cycloalkyl and bicycloelkyl optionally contain one or two of O, S or -N-G wherein G is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or benzyl, wherein each of the above R_5 groups is optionally substituted by from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl, C_1-C_6 alkoxy and trifluoromethyl, or one substituent selected from bromo, iodo, cyano, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), and -SO_2 (C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups optionally contain one double or triple bond and are optionally substituted by one or two substituents independently selected from fluoro, chloro, hydroxy, amino, methylamino, dimethylamino and acetyl;
R_6 is hydrogen or C_1-C_6 alkyl, wherein said C_1-C_6 alkyl is optionally substituted by a single hydroxy, methoxy, ethoxy or fluoro group;
R_7 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, C_1-C_4 alkoxy, -CO(C_1-C_4 alkyl), -CO_2(C_1-

C_4 alkyl), -OCF_3, CF_3, -CH_2OH, -CH_2OCH_3 or -$CH_2OCH_2CH_3$;
R_8 and R_9 are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy or ethoxy;
or R_8 and R_9 together form an oxo (=O) group;
R_{10} is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_n(C_1-C_4 alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl moieties of the foregoing R_{10} groups are optionally substituted by one of hydroxy, trifluoromethyl, amino, carboxy, amido, -NHCO(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro; and,
R_{11} is hydrogen, hydroxy, fluoro, or methoxy.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties or combinations thereof.

The term "alkoxy", as used herein, unless otherwise indicated, includes O-alkyl groups wherein "alkyl" is defined above.

The term "treatment", as used herein, unless otherwise indicated, includes the treatment, prevention, or inhibition of any disorder enumerated within the method of the invention.

More specific compounds for use in the method of the invention include compounds of formula I or II, or pharmaceutically acceptable salts thereof, wherein: B is -NR_1R_2, -NHCHR_1R_2, -$CR_1R_2R_{11}$, -SCHR_1R_2 or -OCHR_1R_2; R_1 is C_1-C_6 alkyl which is optionally substituted with a single hydroxy, fluoro or C_1-C_2 alkoxy group and optionally contains one carbon-carbon double or triple bond; R_2 is benzyl or C_1-C_6 alkyl which optionally contains one carbon-carbon double or triple bond, wherein said C_1-C_6 alkyl and the phenyl moiety of said benzyl are optionally substituted with fluoro, C_1-C_2 alkyl, or C_1-C_2 alkoxy; and R_{11} is hydrogen or fluoro.

Other more specific compounds for use in the method of the invention include compounds of formula I or II, or pharmaceutically acceptable salts thereof, wherein R_2 is (aryl)C_1-C_4 alkyl in which said aryl moiety is phenyl, thienyl, benzofuranyl, furanyl, benzothienyl, thiazolyl, pyridyl or benzothiazolyl.

Other more specific compounds for use in the method of the invention include compounds of formula I or II, or pharmaceutically acceptable salts thereof, wherein B is -NR_1R_2 or -CHR_1R_2 in which R_1 and R_2 are taken together with N or CH to form a 5- or 6-membered ring optionally having sulfur, oxygen, or one more nitrogen in said ring, such as a pyrrolidinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, pyridyl, pyrazinyl or pyrimidyl group.

Other more specific compounds for use in the method of the invention include compounds of formula I or II, or pharmaceutically acceptable salts thereof, wherein B is -NHCHR_1R_2 or -OCHR_1R_2, wherein the CHR_1R_2 moiety is a 5- or 6-membered ring which optionally contains one oxygen or sulfur, such as a tetrahydrofuranyl, tetrahydrothiafuranyl or cyclopentanyl group.

Other more specific compounds for use in the method of the invention include compounds of formula I or II, or pharmaceutically acceptable salts thereof, wherein B is tetrahydrofuranyl, tetrahydrothienyl or thiazolidinyl.

Other more specific compounds for use in the method of the invention include compounds of formula I or II, or pharmaceutically acceptable salts thereof, wherein R_3 is methyl, chloro, or methoxy; R_4 is methyl, -CH_2OH, cyano, trifluoromethoxy, methoxy, trifluoromethyl, chloro, -CO_2CH_3, -CH_2OCH_3, -CH_2Cl, -CH_2F, amino or nitro; R_5 is hydrogen, methylsulfinyl, methylsulfanyl, methylsulfonyl, methyl or ethyl; and R_6 is phenyl or pyridyl wherein said phenyl or pyridyl is substituted by two or three substituents independently selected from fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethyl(C_1-C_2alkoxy)C_1-C_4 alkyl, C_1-C_3 hydroxyalkyl, hydroxy, formyl, -CO_2(C_1-C_2 alkyl), (amino)C_1-C_2 alkyl, -CO(C_1-C_4alkyl), and C_1-C_6 alkyl, wherein said C_1-C_6 alkyl and said C_1-C_4 alkyl are optionally substituted by a single hydroxy, C_1-C_2 alkoxy or fluoro group and optionally contains one carbon-carbon double or triple bond.

For use in the method of the invention, specific compounds of formulas I and II include:

4-(1 -ethyl-propoxy)-2,5-dimethyl-6-(2,4,6-trimethyl-benzyl)-pyrimidine;
2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
2-(4-ethyl-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
3-ethyl-4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine;
2-(2,6-dimethyl-4-propyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
4-(1-ethyl-propoxy)-2-(4-methoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine;
2-(4-ethoxy-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
4-(1-methoxymethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-diethyl-amine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-propyl-amine;
[2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-4-yl](1-ethyl-propyl)-amine;

butyl-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine;
4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)pyridine;
butyl-[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-amine;
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester;
[3,6-dimethyl-[2-(2,4,6-trimethyl-phenylsulfanyl)-pyridin-4-yl]-ethyl-propyl-amine;
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-methanol;
[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-propyl-amine;
1-(ethyl-propyl)-[6-methyl-3-nitro-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine;
N4-(1-ethyl-propyl)-6-methyl-3-nitro-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,4-diamine;
N4-(1-ethyl-propyl)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;
N4-(1-ethyl-propyl)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridin-2,3,4-triamine;
3,6-dimethyl-2-(2,4,6-trimethy-phenoxy)-pyridin-4-yl]-ethyl-(2,2,2-trifluoro-ethyl)-amine;
[3-chloromethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)pyridin-4-yl]-(1-ethyl-propyl)-amine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine;
(1-ethyl-propyl)-[2-methyl-5-nitro-6-(2,4,6-trimethyl-pyridin-3-yloxy)-pyrimidin-4-yl]-amine;
(1-ethyl-propyl)-[3-methoxymethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine;
N-(1-ethyl-propyl)-2-methyl-5-nitro-N'-(2,4,6-trimethyl-pyridin-3-yl)-pyrimidine-4,6-diamine;
[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-diethyl-amine;
4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;
butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethyl-amine;
4-(butyl-ethylamino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo [2,3-d]pyrimidin-6-one;
4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;
N-butyl-N-ethyl-2,5-dimethyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine;
(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo [4,5-b]pyridin-7-yl]-amine;
[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;
N4-(1-ethyl-propyl)-6,N3-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;
N-4-(1-ethyl-propyl)-6,N3,N3-trimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;
6-(1-ethyl-propoxy)-2-methyl-N4-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5-diamine;
[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine; and
6-(ethyl-propyl-amino)-2,7-dimethyl-9-(2,4,6-trimethylphenyl)-7,9-dihydro-purin-8-one.

For use in the method of the invention, specific compounds of formula II wherein E and D are connected by a double bond, E is $-CR_4$, D is $-CR_{10}$ or N, Y is N, and A is $-CR_7$, include:

butyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-ethylamine;
3,6-dimethyl-4-(tetrahydrofuran-3-yloxy)-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridine;
[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1 H-pyrazolo [3,4,b]pyridin-4-yl]-(1methoxymethylpropyl)-amine;
4-(1-methoxymethylpropoxy)-3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridine;
(1-ethylpropyl)-[3,5,6-trimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-amine
4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine;
4-(1-ethylpropoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-b]pyridine; and
4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,6-dimethyl-4-bromophenyl)-7H-pyrrolo [2,3-b]pyridine.

For use in the method of the invention, specific compounds of formula II wherein E and D are connected by a double bond, E is $-CR_4$, and D, Y and A are N, include:

3-[(4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino]-propan-1-ol;
diethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
2-[butyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino]-ethanol;
dibutyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d] pyrimidin-4-yl]-amine;
butyl-cyclopropylmethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
di-1-propyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
diallyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-chloro-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-methoxy-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1 H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
4-(1-ethyl-propyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine;
2-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamine]-butan-1-ol;
[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo-[3,4-d] pyrimidin-4-yl]-(1-methylpropyl)amine; and
4-(1-methoxymethylpropoxy)-3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine.

For use in the method of the invention, specific compounds of formula II wherein E and D are connected by a double bond, E is -CR_4-, D is -CR_{10}-, and Y and A are N, include:

n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
di-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d] pyrimidin-4-yl]amine;
diethyl-2 5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
n-butyl-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2-[N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-ethanol;
4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2,3-d] pyrimidin-4-yl]amine;
2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidyl-4-yl]-(1-ethyl-propyl)amine;
2-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
2-(S)-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
4-(1-ethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
4-(1-methoxymethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
4-(1-ethyl-butyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo-[2,3-d]pyrimidine;
[7-(4-bromo-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-(1-methoxymethyl-propyl)-amine;
2-[7-(2-bromo-4,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
2-[7-(4-ethyl-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
2-[7-(2-ethyl-4,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol; and
2-[7-(2-fluoromethyl-4,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol.

The method of the invention further comprises the treatment of stroke by administering to a mammal, including a human, in need of such treatment a therapeutically effective amount of a compound of formula II, referred to above, or a pharmaceutically acceptable salt thereof, wherein a double bond connects E and D, D is -CR_{10}- or N, E is -CR_4-, and Y and A are N. Compounds of formula III, provided below, are the compounds of formula II wherein a double bond connects E and D, D is -CR_{10}- or N, E is -CR_4-, and Y and A are N. The compounds of formula III are provided below in the claims and are directed to the treatment of stroke.

Whenever reference is made herein to 3- to 8-membered cycloalkyl or 3- to 12-membered bicycloalkyl optionally containing one or two of O, S, or -N-G, it is understood that the oxygen and sulfur atoms are not adjacent to each other in the cycloalkyl or bicycloalkyl ring system. The three membered cycloalkyl optionally contains just one of O, S, or -N-G. An example of a six-membered cycloalkyl having O and NH is morpholinyl.

Whenever R_2 or R_5 is a heterocyclic group, the attachment of the group is through a carbon atom.

In the compounds of formulas I and II, referred to above, certain aminal or acetal moieties may not be sufficiently stable for use in the method of the invention. Such unstable compounds may include, for example, a compound of formula I or II wherein B is -NR_1R_2 and R_1 is -CH(OH)CH_3. Such unstable compounds will be apparent to those skilled in the art and do not form part of the invention.

Formulas I and II, referred to above, are intended to include all stereoisomers (e.g., all geometric and optical isomers) as well as racemates of all individual compounds within the depicted genus.

Detailed Description of the Invention

The compounds of formulas I and II, and their pharmaceutically acceptable salts, are readily prepared. The compounds of formula II wherein A, D and Y are N, a double bond connects E and D, and E is -CR_4-, are prepared by one or more of the synthetic methods referred to in United States patent application serial number 08/481,13, referred to above. The compounds of formula II wherein A and Y are N, a double bond connects E and D, E is -CR_4-, and D is -CR_{10}-, are prepared by one or more of the synthetic methods referred to in United States patent application serial number 08/448,539, referred to above. The compounds of formula II wherein A is -CR_7, a double bond connects E and D, E is -CR_4-, D is N or -CR_{10}-, and Y is N, are prepared by one or more of the synthetic methods referred to in PCT international application number PCT/IB95/00373, referred to above. The remaining compounds of formula II and

the compounds of formula I are prepared by one or more of the synthetic methods referred to in PCT international application number PCT/IB95/00439, referred to above.

Pharmaceutically acceptable salts of the compounds of formulas I and II include salts of acidic or basic groups. For example, pharmaceutically acceptable salts include sodium, calcium and potassium salts of acidic groups, such as when the R_{10} substituent is carboxy. Such salts are generally prepared by combining a compound of formula I or II with one molar equivalent of NaOH or KOH in a suitable solvent. Pharmaceutically acceptable acid addition salts of basic groups, such as amino groups, are formed by reacting the base form of a compound of formula I or II with an appropriate acid. Pharmaceutically acceptable salts of basic groups include hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogen phosphate, acetate, succinate, citrate, tartrate, lactate, mandelate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), at least one molar equivalent and usually a molar excess of the acid is employed. However, when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration or addition of a non-solvent.

In the method of the invention, the compounds of formulas I and II, and their pharmaceutically acceptable salts, can be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. The pharmaceutical compositions formed by combining the active compounds and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type can also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof. Oral administration is generally preferred. However, if the patient is unable to swallow, or oral absorption is otherwise impaired, another route of administration such as suppositories, parenteral (i.m., i.v.), or topical administration will be appropriate.

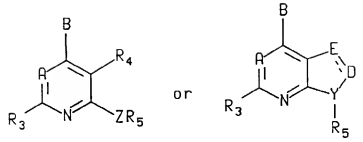
For parenteral administration, solutions of the active compound in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution can be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

In the method of the invention, the effective dosage for the compounds of formulas I and II, and their pharmaceutically acceptable salts, depends on the intended route of administration and other factors such as age and weight of the patient, as generally known to a physician. The dosage also depends on the illness to be treated. In general, the daily dosage will generally range from about 0.1 to 50 mg/kg of the body weight of the patient to be treated. The daily dosage may be given in a single dose or up to three divided doses. In the prevention of premature birth, the dosage should be administered daily after high levels of corticotropin-releasing hormone have been detected early in pregnancy and then discontinued just prior to the end of the term for normal pregnancy.

The methods for testing the compounds of formulas I and II, and their pharmaceutically acceptable salts, for CRF antagonist activity are as described in Endocrinology, 116, 1653-1659 (1985) and Peptides 10, 179-188 (1989) which determine the binding affinity of a test compound for a CRF receptor. The binding affinities for the active compounds, expressed as IC_{50} values, generally range from about 0.2 nanomolar to about 10 micromolar.

Claims

1. The use of a compound of the formula



I II

or a pharmaceutically acceptable salt thereof, wherein

the dashed line represents an optional double bond;

A is -CR_7 or N;

B is -NR_1R_2, -$CR_1R_2R_{11}$, -C(=CR_1R_{12})R_2, -NHC$R_{11}R_1R_2$, -OC$R_{11}R_1R_2$, -S$CR_{11}R_1R_2$, -$CR_{11}R_2OR_1$, -$CR_{11}R_2SR_1$, -C(S)R_2, -$NHNR_1R_2$, -$CR_2R_{11}NHR_1$ or -C(O)R_2;

D is: (i) N or -CR_{10} when a double bond connects E and D and E is -CR_6; (ii) -CR_{10} when a double bond connects E and D and E is N; or (iii) -CR_6R_9, -CHR_{10}, -C=O, -C=S, -C=NH, or -C=NCH_3 when a single bond connects E and D;

E is -CR_4 or N when a double bond connects E and D, and E is -CR_4R_6 or -NR_6 when a single bond connects E and D;

Y is N or -CH;

Z is NH. O, S, -N(C_1-C_2 alkyl) or -$CR_{12}R_{13}$, wherein R_{12} and R_{13} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{12} and R_{13} is cyano and the other is hydrogen or methyl;

R_1 is hydrogen or C_1-C_6 alkyl which is optionally substituted with one or two substituents independently selected from hydroxy, cyano, nitro, fluoro, chloro, bromo, iodo, CF_3, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -CO_2(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, and (C_1-C_4 alkyl)sulfanyl, and wherein said C_1-C_6 alkyl, C_1-C_4 alkoxy and the C_1-C_4 alkyl moieties in the foregoing R_1 groups optionally contain one double or triple bond;

R_2 is C_1-C_6 alkyl, aryl or (aryl)C_1-C_4 alkyl wherein said aryl and the aryl moiety of said (aryl)C_1-C_4 alkyl are selected from the group consisting of phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, and benzoxazolyl; or R^2 is C_3-C_8 cycloalkyl or (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said (C_3-C_8 cycloalkyl)C_1-C_6 alkyl having at least 4 ring members is optionally replaced by an oxygen or sulfur atom or by -NR_{14} wherein R_{14} is hydrogen or C_1-C_4 alkyl; and wherein each of the foregoing R_2 groups is optionally substituted by from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or by one substituent selected from bromo, iodo, cyano, nitro, C_1-C_6 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfinyl, and (C_1-C_4 alkyl)sulfonyl, and wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_2 groups optionally contain one carbon-carbon double or triple bond;

or R^1 and R^2 of said -NR_1R_2 and said -$CR_1R_2R_{11}$ are taken together to form a saturated 5 to 8 member ring, wherein said ring optionally contains one or two carbon-carbon double bonds, and wherein one or two of the ring carbons is optionally replaced by an oxygen or sulfur atom;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, SH, -NH(C_1-C_4 alkyl'),-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CH_2OH, -CH_2OCH_3, -O(C_1-C_4 alkyl), (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfonyl, or (C_1-C_4 alkyl) sulfinyl, wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl moieties of the foregoing R_3 groups optionally contain one double or triple bond and are optionally substituted by from one to three substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, -NH(C_1-C_2 alkyl), -N(C_1-C_2)$_2$, -$NHCOCH_3$, fluoro, chloro and C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, trifluoromethoxy, -CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -CH_2CF_3, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -N(CH_3)$_2$, -$NHCOCH_3$, -$NHCONHCH_3$, (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, cyano, hydroxy -CO(C_1-C_4

alkyl), -CHO, or -CO_2(C_1-C_4 alkyl), wherein said C_1-C_6 alkyl, C_1-C_6 alkoxy and the C_1-C_4 alkyl moieties of the foregoing R_4 groups optionally contain one double or triple bond and are optionally substituted with one substituent selected from hydroxy, amino, -$NHCOCH_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -CO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, (C_1-C_3 alkyl)sulfany, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl, pyridinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, wherein said cycloalkyl and bicycloalkyl optionally contain one or two of O, S or -N-G wherein G is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or benzyl, wherein each of the above R_5 groups is optionally substituted by from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl, C_1-C_6 alkoxy and trifluoromethyl, or one substituent selected from bromo, iodo, cyano, nitro, amino, - NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2 -$NHSO_2$(C_1-C_4 alkyl), - S(C_1-C_4 alkyl), and -SO_2($C_1$$C_4$ alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups optionally contain one double or triple bond and are optionally substituted by one or two substituents independently selected from fluoro, chloro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R_6 is hydrogen or C_1-C_6 alkyl, wherein said C_1-C_6 alkyl is optionally substituted by a single hydroxy, methoxy, ethoxy or fluoro group;

R_7 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, C_1-C_4 alkoxy, -CO(C_1-C_4 alkyl), -CO_2 (C_1-C_4 alkyl), -OCF_3, CF_3, -CH_2OH, -CH_2OCH_3 or -$CH_2OCH_2CH_3$;

R_8 and R_9 are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy; or R_8 and R_9 together form an oxo (=O) group;

R_{10} is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_n(C_1-C_4 alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl moieties of the foregoing R_{10} groups are optionally substituted by one of hydroxy, trifluoromethyl, amino, carboxy, amido, -NHCO(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro; and,

R_{11} is hydrogen, hydroxy, fluoro, or methoxy; for the preparation of a medicament for treating a disorder selected from the group consisting of cardiovascular or heart related diseases including hypertension, tachycardia, and congestive heart failure, osteoporosis, premature birth, psychosocial dwarfism, stress-induced fever, ulcer, diarrhea, post-operative ileus, and colonic hypersensitivity associated with psychopathological disturbance and stress.

2. The use of claim 1 wherein B is -NR_1R_2, -$NHCHR_1R_2$, -$CR_1R_2R_{11}$, -$SCHR_1R_2$ or -$OCHR_1R_2$; R_1 is $C_1$$C_6$ alkyl which is optionally substituted with a single hydroxy, fluoro or C_1-C_2 alkoxy group and optionally contains one carbon-carbon double or triple bond; R_2 is benzyl or C_1-C_6 alkyl which optionally contains one carbon-carbon double or triple bond, wherein said C_1-C_6 alkyl and the phenyl moiety of said benzyl are optionally substituted with fluoro, C_1-C_2 alkyl, or C_1-C_2 alkoxy; and R_{11} is hydrogen or fluoro.

3. The use of claim 1 wherein R_2 is (aryl)C_1-C_4 alkyl in which said aryl moiety is phenyl, thienyl, benzofuranyl, furanyl, benzothienyl, thiazolyl, pyridyl or benzothiazolyl.

4. The use of claim 1 wherein B is NR_1R_2 or CHR_1R_2 in which R_1 and R_2 are taken together with N or CH to form a 5- or 6-membered ring optionally having sulfur, oxygen, or, where B is NR_1R_2, one more nitrogen in said ring.

5. The use of claim 1 wherein B is -$NHCHR_1R_2$ or -$OCHR_1R_2$, wherein the CHR_1R_2 moiety is a 5- or 6-membered ring which optionally contains one oxygen or sulfur.

6. The use of claim 6 wherein B is tetrahydrofuranyl, tetrahydrothiafuranyl or cyclopentanyl.

7. The use of claim 6 wherein B is tetrahydrofuranyl, tetrahydrothienyl or thiazolidinyl.

8. The use of claim 1 wherein R_3 is methyl, chloro, or methoxy; R_4 is methyl, -CH_2OH, cyano, trifluoromethoxy, methoxy, trifluoromethyl, chloro, -CO_2CH_3, -CH_2OCH_3, -CH_2Cl, -CH_2F, amino or nitro; R_6 is hydrogen, methylsulfinyl, methylsulfanyl, methylsulfonyl, methyl or ethyl; and R_5 is phenyl or pyridyl wherein said phenyl or pyridyl is substituted by two or three substituents independently selected from fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethyl,(C_1-C_2 alkoxy)C_1-C_4 alkyl, C_1-C_3 hydroxyalkyl, hydroxy, formyl, -CO_2(C_1-C_2 alkyl), (amino)C_1-C_2

alkyl, -CO(C_1-C_4 alkyl) , and C_1-C_6 alkyl, wherein said C_1-C_6 alkyl and said C_1-C_4 alkyl are optionally substituted by a single hydroxy, C_1-C_2 alkoxy or fluoro group and optionally contains one carbon-carbon double or triple bond.

9. The use of claim 1 wherein the compound of formula I or II is selected from the group consisting of:

4-(1-ethyl-propoxy)-2,5-dimethyl-6-(2,4,6-trimethyl-benzyl)-pyrimidine;
2-(4-bromo-2,6-dimethyl-phenoxy)4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
2-(4-ethyl-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
3-ethyl-4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine;
2-(2,6-dimethyl-4-propyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
4-(1-ethyl-propoxy)-2-(4-methoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine;
2-(4-ethoxy-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;
4-(1-methoxymethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-diethyl-amine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-propyl-amine;
[2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-4-yl] (1-ethyl-propyl)-amine;
butyl-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine;
4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridine;
butyl-[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-amine,
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester;
[3,6-dimethyl-[2-(2,4,6-trimethyl-phenylsulfanyl)-pyridin-4-yl]-ethyl-propyl-amine;
4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-methanol;
[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-propyl-amine;
1-(ethyl-propyl)-[6-methyl-3-nitro-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine;
N4-(1-ethyl-propyl)-6-methyl-3-nitro-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,4-diamine;
N4-(1-ethyl-propyl)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;
N4-(1-ethyl-propyl)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine;
3,6-dimethyl-2-(2,4,6-kimethyl-phenoxy)-pyridin-4-yl]-ethyl-(2,2,2-trifluoro-ethyl)-amine;
[3-chloromethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)pyridin-4-yl]-(1-ethyl-propyl)-amine;
[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine;
(1-ethyl-propyl)-[2-methyl-5-nitro-6-(2,4,6-trimethyl-pyridin-3-yloxy)-pyrimidin-4-yl]-amine;
(1-ethyl-propyl)-[3-methoxymethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine;
N-(1-ethyl-propyl)-2-methyl-5-nitro-N'-(2,4,6-trimethyl-pyridin-3-yl)-pyrimidine-4,6-diamine;
[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-diethyl-amine;
4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;
butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo [2,3-d]pyrimidin-4-yl]-ethyl-amine;
4-(butyl-ethylamino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pydmidin-6-one;
4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;
N-butyl-N-ethyl-2,5-dimethyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine;
(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-amine;
[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-(1-ethylpropyl)-amine;
N4-(1-ethyl-propyl)-6,N3-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;
N4-(1-ethyl-propyl)-6,N3,N3-trimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;
6-(1-ethyl-propoxy)-2-methyl-N4-(2,4,6-trimethylphenyl)-pyrimidine-4,5-diamine;
[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine;
6-(ethyl-propyl-amino)-2,7-dimethyl-9(2,4,6-trimethylphenyl)-7,9-dihydro-purin-8-one, and pharmaceutically acceptable salts of the foregoing compounds.

10. The use of claim 1 wherein said compound is a compound of formula II in which E and D are connected by a double bond, E is -CR_4, D is -CR_{10} or N, Y is N, and A is -CR_7.

11. The use of claim 10 wherein said compound is selected from the group consisting of:

butyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-ethylamine;
3.6-dimethyl-4-(tetrahydrofuran-3-yloxy)-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridine
[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4,b]pyridin-4-yl]-(1-methoxymethylpropyl)-amine;
4-(1-methoxymethylpropoxy)-3,6-dimethyl-1-(214,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridine;

(1-ethylpropyl)-[3,5,6-trimethyl-1(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-b]pyridin-4-yl]-amine;
4-(1-ethylpropoxy)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo [2,3-b]pyridine;
4-(1 -ethylpropoxy)-2,5,6-trimethyl-7-(2,4,6-[2,3-b]pyridine;
4-(1-ethylpropoxy)-2,5dimethyl-7-(2,6-dimethyl-4-bromophenyl)-7H-pyrrolo[2,3-b]pyridine, and pharmaceutically acceptable salts of the foregoing compounds.

12. The method of claim 1 wherein said compound is a compound of formula II in which E and D are connected by a double bond, E is -CR_4, and D, Y and A are N.

13. The use of claim 12 wherein said compound is selected from the group consisting of:

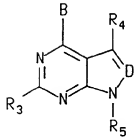
3-[(4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino]propan-1-ol,
diethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1 H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
2-{butyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethanol;
dibutyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-cyclopropylmethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
di-1-propyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
diallyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-chloro-3-methylsulfanyl-1-(2,4 6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
butyl-ethyl-[6-methoxy-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;
propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d] pyrimidin-4-yl]-amine;
4-(1-ethyl-propyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d] pyrimidine;
2-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamine]-butan-1-ol;
[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo-[3,4-d] pyrimidin-4-yl]-(1-methylpropyl)amine;
4-(1 -methoxymethylpropoxy)-3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine, and pharmaceutically acceptable salts of the foregoing compounds.

14. The use of claim 1 wherein said compound is a compound of formula II in which E and D are connected by a double bond, E is -CR_4, D is -CR_{10}, and Y and A are N.

15. The use of claim 14 wherein said compound is selected from the group consisting of:

n-butyl-ethyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
di-n-propyl-[2,5-dimethyl-7-(2,4 6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
ethyl-n-propyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
diethyl-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo [2,3-d]pyrimidin-4-yl]amine;
n-butyl-ethyl-[2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2-{N-n-butyl-N-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amino}-ethanol;
4-(1-ethyl-propyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
n-butyl-ethyl-[2,5-dimethyl-7-(2,4-dimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]amine;
2,5-dimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidyl-4-yl]-(1-ethyl-propyl)amine;
2-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
2-(S)-[7-(4-bromo-2,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
4-(1-ethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
4-(1-methoxymethyl-propoxy)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine;
4-(1-ethyl-butyl)-2,5,6-trimethyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo-[2,3-d]pyrimidine;
[7-(4-bromo-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-(1-methoxymethyl-propyl)-amine;
2-[7-(2-bromo-4,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
2-[7-(4-ethyl-2,6-dimethyl-phenyl)-2,5-dimethyl-7H-pyrrolo [2,3-d] pyrimidin-4-ylamino]-butan-1-ol;
2-[7-(2-ethyl-4,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino]-butan-1-ol;
2-[7-(2-fluoromethyl-4,6-dimethylphenyl)-2,5-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino]-butan-1-ol, and pharmaceutically acceptable salts of the foregoing compounds.

16. The use of a compound of the formula



III

or a pharmaceutically acceptable salt thereof, wherein

B is $-NR_1R_2$,$-CR_1R_2R_{11}$,$-C(=CR_1R_{12})R_2$,$-NHCR_{11}R_1R_2$, $-OCR_{11}R_1R_2$, $-SOR_{11}R_1R_2$, $-CR_{11}R_2OR_1$, $-CR_{11}R_2SR_1$, $-C(S)R_2$, $-NHNR_1R_2$, $-CR_2R_{11}NHR_1$ or $-C(O)R_2$;

D is N or $-CR_{10}$;

R_1 is hydrogen or C_1-C_6 alkyl which is optionally substituted with one or two substituents independently selected from hydroxy, cyano, nitro, fluoro, chloro, bromo, iodo, CF_3, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4alkyl)CO($C_1$$C_4$ alkyl), -NHCO(C_1-C_4 alkyl), -CO_2(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, and (C_1-C_4 alkyl)sulfanyl, and wherein said C_1-C_6 alkyl, C_1-C_4 alkoxy and the C_1-C_4 alkyl moieties in the foregoing R_1 groups optionally contain one double or triple bond;

R_2 is C_1-C_6 alkyl, aryl or (aryl)C_1-C_4 alkyl wherein said aryl and the aryl moiety of said (aryl)C_1-C_4 alkyl are selected from the group consisting of phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl. pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benziisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, and benzoxazolyl; or R^2 is C_3-C_8 cycloalkyl or (C_3-C_8 cycloalkyl)C_1-C_6 alkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said (C_3-C_8 cycloalkyl)C_1-C_6 alkyl having at least 4 ring members is optionally replaced by an oxygen or sulfur atom or by $-NR_{14}$ wherein R_{14} is hydrogen or C_1-C_4 alkyl; and wherein each of the foregoing R_2 groups is optionally substituted by from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or by one substituent selected from bromo, iodo, cyano, nitro, C_1-C_8 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfinyl, and (C_1-C_4 alkyl)sulfonyl, and wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_2 groups optionally contain one carbon-carbon double or triple bond;

or R^1 and R^2 of said $-NR_1R_2$ and said $-CR_1R_2R_{11}$ are taken together to form a saturated 5 to 8 member ring, wherein said ring optionally contains one or two carbon-carbon double bonds, and wherein one or two of the ring carbons is optionally replaced by an oxygen or sulfur atom;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, SH, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), $-CH_2OH$, $-CH_2OCH_3$, -O(C_1-C_4 alkyl), (C_1-C_4 alkyl)sulfanyl, (C_1-C_4alkyl)sulfonyl, or (C_1-C_4 alkyl)sulfinyl, wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl moieties of the foregoing R_3 groups optionally contain one double or triple bond and are optionally substituted by from one to three substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, -NH(C_1-C_2 alkyl), -N(C_1-C_2)$_2$, $-NHCOCH_3$, fluoro, chloro and C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, trifluoromethoxy,$-CH_2OCH_3$, $CH_2OCH_2CH_3$ $-CH_2CH_2OCH_3$,$-CH_2CF_3$, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -N(CH_3)$_2$, $-NHCOCH_3$, $-NHCONHCH_3$, (C_1-C_4 alkyl)sulfanyl, (C_1-C_4 alkyl)sulfinyl, (C_1-C_4 alkyl)sulfonyl, cyano, hydroxy -CO(C_1-C_4 alkyl), -CHO, or -CO_2(C_1-C_4 alkyl), wherein said C_1-C_6 alkyl, C_1-C_6 alkoxy and the C_1-C_4 alkyl moieties of the foregoing R_4 groups optionally contain one double or triple bond and are optionally substituted with one substituent selected from hydroxy, amino, $-NHCOCH_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -CO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, (C_1-C_3 alkyl)sulfanyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, morpholinyl,

pyridinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, wherein said cycloalkyl and bicycloalkyl optionally contain one or two of O, S or -N-G wherein G is hydrogen, C_1-C_4 alkyl. C_1-C_4 alkanoyl, phenyl or benzyl, wherein each of the above R_5 groups is optionally substituted by from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl, C_1-C_6 alkoxy and trifluoromethyl, or one substituent selected from bromo, iodo, cyano, nitro, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -NHSO_2(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups optionally contain one double or triple bond and are optionally substituted by one or two substituents independently selected from fluoro, chloro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R_{10} is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, formyl, amino, -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_n(C_1-C_4 alkyl), wherein n is 0, 1 or 2, cyano, carboxy, or amido, wherein said C_1-C_6 alkyl and the C_1-C_4 alkyl moieties of the foregoing R_{10} groups are optionally substituted by one of hydroxy, trifluoromethyl, amino, carboxy, amido, -NHCO(C_1-C_4 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -CO_2(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro; and,

R_{11} is hydrogen, hydroxy, fluoro, or methoxy;

for the preparation of a medicament for treating patients who have suffered a stroke.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 96 30 7977

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	WO-A-94 13677 (PFIZER ;CHEN YUHPYNG LIANG (US)) 23 June 1994 * the whole document * ---	1-16	A61K31/435 A61K31/44 A61K31/445 A61K31/505
X	WO-A-94 13676 (PFIZER ;CHEN YUHPYNG L (US)) 23 June 1994 * the whole document * ---	1-16	
P,X	EP-A-0 691 128 (PFIZER) 10 January 1996 * the whole document * ---	1-16	
P,X, D	WO-A-95 33750 (PFIZER ;CHEN YUHPYNG L (US)) 14 December 1995 * the whole document * -----	1-16	

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

A61K

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
MUNICH	15 January 1997	Herrera, S

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office EP 96 30 7977 - C -

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extend that it is not possible to carry out a meaningfull search into state of the art on the basis of some of the claims.

Claims searched completely:
Claims searched incompletely: 1-16
Claims not searched:

Reason for the limitation of the search: The use of the compounds defined in the present claims for the treatment of the medical indication given in claims 1 and 16 appears to solely hypothetical. The applicant has not given any evidence the firstly the given indications have anything to do with CRF, nor that they can be treated with any CRF antagonist. The search has therefore been limited to the general inventive concept, i.e. the use of the defined compounds as CRF antagonists.